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GREEN SYNTHESIS OF NEW HYDRAZONE DERIVATIVES

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Abstract:

Novel set of hippuric hydrazones (6-9) bearing indole and quinoline moieties were synthesized in three steps following the protocol of microwave irradiation and solvent-free conditions. The first series were synthesized by irradiate ethyl hippurate (3) with 1H-indole-6-carbaldehyde (4) under solvent-free conditions. The second series were synthesized by irradiate ethyl hippurate (3) with substituted 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (5) under solvent-free conditions. This work aims to develop new synthetic route of hippuric hydrazones which may possess a promising biological activities against covid-19. The formation of the prepared heteroaromatic hydrazones were approved by spectral 1H NMR, IR and mass data.

Keywords: Hydrazone, Microwave, Solvent-Free Conditions.

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Introduction:

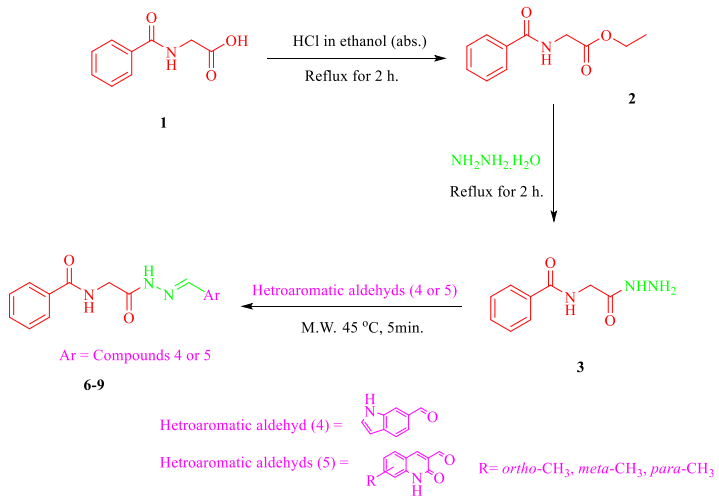
The chemistry of hydrazones has become increasingly important subject particularly in the field of drugs[1-3]. These compounds were confirmed to possess significant biological activity against a variety of diseases [4]. The moiety $R_1R_2C=N-NH_2$ in the skeleton of these compounds is behind the biological characteristics of hydrazones [5-11]. On the other hand, these compounds exhibition considerable activities for healing certain diseases especially prion diseases [12], tuberculosis [13], influenza virus H5N1[14], SARS-CoV-2 [15] and HIV [16,17]. The synthesis of hydrazones consist of reacting various aromatic aldehydes with hydrazines/ hydrazides in the presence of protic solvents [18,19]. Due to the high reactivity of these compound toward electrophiles and nuclophiles they have the ability to converted to numerous heterocyclic compounds which may increase their biological activities [20]. Hippuric hydrazones were confirmed to possess respectable biological activity toward certain diseases [21,22]. In our previous work, we have synthesized some of hippuric hydrazones by following the microwave method as an efficient and green protocol which is environmentally and economically desirable [23]. Here we are using the same protocol to synthesis a new set of hippuric hydrazones which consist of indole and quinoline moieties in their skeletons. These moieties can exist in various natural products and possess valuable biological activities[24,25]. Therefore, synthesizing hydrazones containing these moieties may show a promising biological activities against covid-19 which will be our next investigation.

Experimental

All chemicals and starting materials were obtained from different commercial supplier. The determination of melting point were obtained by (Gallenkamp melting point machine). All microwave reactions were carried out using (Smith Creator™ optimizer). All ^1H NMR were analyzed using (Bruker 400 MHz). The accurate mass analysis for the synthesized compounds were recorded by (Micro Mass LCT operating in Electrospray mode (ES). All IR spectra data were achieved using (Bruker Tensor 27 spectrometer) using KBr discs. Hippuric hydrazide (3) was prepared by following the reported procedure [26], Compound (4) was prepared according to the reported procedures [27 and 28]. The aromatic aldehydes (5) were synthesized following the mentioned elsewhere procedure [29]. Scheme (1).

Microwave protocol for synthesis of heteroaromatic hippuric hydrazones (11-14)

The same amount of moles (0.1 M) of hippuric hydrazide (3) and hetroaromatic aldehydes (4) or (5) (were mixed in a 20 ml microwave vial. For five minutes, the sample vial was irradiated and heated to 45^{o}C (17 bar). The mixture vial was then left to cool at ambient temperature. Slowly, an ice-cooled water was added to the mixture. The formed crude product was collected and dried. The crude product was then purified by recrystallization using ethanol-water (2:1) affording the pure product as pall yellow solid, Scheme (1).



Scheme 1: the synthesis of hippuric hydrazones (6-9)

Results and discussions

New set of novel hippuric hydrazones bearing indole and quinoline moieties were synthesized following the microwave irradiation protocol and without using any solvents. This protocol was used in our previous work for synthesizing different types of hippuric hydrazones [23]. The results obtained were comparable to those obtained in our published work. Table 1.

Table (1): conditions used for synthesis hetroaromatic hippuric hydrazones 6-9

Compound No.	Batch yield. %	Batch time./ h.	MW. Yield. %	MW. Time./min.
6	61	3	94	5
7	65	3	92	5
8	63	3	96	5
9	64	3	93	5

It is obvious that 92-96 % of the pure products were obtained at only five minutes when applying the reaction under microwave irradiation and without using any solvent, whereas applying the same reaction using the conventional batch conditions affords only 61-65 % of the pure products.

The investigation was also included the use of solvents for the synthesis of hydrazones (6-9). In microwave protocol, protic solvents such as methanol and ethanol were used as a reaction media, it was found that low percentage yield of the pure products was obtained. Increasing the temperature up to 50 °C (20 bar) did not affect the product yield even when the time of the reaction was increased up to 10 minutes. As a result, it was found that the optimal condition to obtain the above percentage yields is running the reaction at 45 °C (17 bar) under microwave condition for five minutes and without using any solvent.

Conclusions

In this study, a novel set of hippurc hydrazones bearing indole and quinolone moieties in their skeleton has been designed and prepared. These compounds were prepared using the microwave protocol which considered as a green, economic, clean and environmental method. No solvents were used and high percentage yield of the pure products was achieved. The aim

of this work is to synthesis these types of hydrazones which may have a medical application particularly against covid-19 which will be our next exploration.

(*E*)-*N*-(2-(2-((1H-indol-6-yl)methylene)hydrazineyl)-2-oxoethyl)benzamide **(6)**

Pall yellow solid. mp.: 169-171 °C. FTIR spectrum, (ν_{max}/ cm^{-1}): 3427 (NH for indole), 3422 for NH, 3408 for NH, 3062 for Ar-CH, 2919 for aliphatic-CH, 1701, 1640 for C=O, 1622 for C=N, 1598, 1487 for C-H, 1362 for CN. ^{1}H NMR using deuterated DMSO as a solvent: δ12.3 bs,1H for N-H, 9.9 s, 1H for NH indole, 8.4 s, 1H for N-H, 8.1-8.0 m, 10 aromatic-H., s, 1H., C-H, 5.6, 5.4 s, 2H, for CH_2. Low resolution mass spectrum (Electrospray) m/z: 321 100%, $\{M+H\}^+$.

(*E*)-*N*-(2-(2-((6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazineyl)-2-oxoethyl)benzamide **(7)**

Pall yellow soild. mp.: 180-182 °C. FTIR spectrum, (ν_{max}/ cm^{-1}): 3402 N-H, 3332 for NH, 3304 for NH, 3031 for Ar-CH, 2896 for aliphatic-CH, 1712, 1638 for C=O, 1624 for C=N, 1591, 1482 for C-H, 1359 for CN. ^{1}H NMR using deuterated DMSO as a solvent: δ12.4 bs,1H for N-H, 9.7 s, 1H for N-H quinoline, 8.1 s, 1H for N-H, 8.5-7.4 m, 9 aromatic-H, s, 1H, CH, 5.4, 5.1 s, 2H for CH_2, 2.5 s,3H for CH_3. Low resolution mass spectrum (Electrospray) m/z: 363 100%, $\{M+H\}^+$.

(*E*)-*N*-(2-(2-((7-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazineyl)-2-oxoethyl)benzamide **(8)**

Pall yellow solid. mp.: 189-190 °C. FTIR spectrum, (ν_{max}/ cm^{-1}): 3432 (NH), 3339 for (NH), 3309 for (NH), 3029 for (Ar-CH), 2898 for (aliphatic-CH), 1717, 1632 for (C=O), 1620 for (C=N), 1598, 1479 for (C-H), 1361 for (CN). ^{1}H NMR using deuterated DMSO as a solvent: δ12.2 bs,1H for (N-H), 9.8 s, 1H for (N-H) quinoline, 8.1 s, 1H for (N-H), 8.6-7.9 m, 9 aromatic-H, s, 1H, (C-H), 5.6, 5.4 s, 2H for (CH_2), 2.5 s,3H for (CH_3). Low resolution mass spectrum (Electrospray) m/z: 363 100%, $\{M+H\}^+$.

(*E*)-*N*-(2-(2-((8-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazineyl)-2-oxoethyl)benzamide **(9)**

Pall yellow solid. mp.: 174-176 °C. IR (KBr), (ν_{max}/cm^{-1}): 3412 (NH), 3341 for (NH), 3312 for (NH), 3030 for (Ar-CH), 2889 for aliphatic-CH, 1718, 1641 for (C=O), 1628 for (C=N), 1598, 1487 for (C-H), 1367 for (CN). ^{1}H NMR using deuterated DMSO as a solvent: δ12.4 bs,1H for (N-H), 9.7 s, 1H for (N-H) quinoline, 8.4 s, 1H for (N-H), 8.6-7.2 m, 9 aromatic-H, s, 1H, (CH), 5.4, 5.2 s, 2H for (CH_2), 2.5 s,3H for (CH_3). Low resolution mass spectrum (Electrospray) m/z: 363 100%, $\{M+H\}^+$.

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